Remarks

Claims 1-37 are pending in the application. Claim 1-21 and 30-37 are withdrawn from consideration as directed to a non-elected invention. Claims 22-29 are presently under examination.

Regarding the Rejections under 35 U.S.C. § 112, First Paragraph

Written Description

Applicants traverse the rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Base claim 22 is directed to a method of identifying a therapeutic agent for treating Alzheimer's disease by performing matings between a first parent strain carrying a mutation in an Alzheimer's disease gene and a second parent strain containing a genetic variation, whereby test progeny are produced, where, in the absence of an agent, the parent strains produce test progeny having an altered phenotype relative to at least one sibling control; administering an agent to at least one strain selected from the group consisting of the first parent strain, the second parent strain and the test progeny; and assaying the test progeny for the altered phenotype, wherein a modification of the altered phenotype producing a phenotype with more similarity to a wild type phenotype than the altered phenotype has to the wild type phenotype indicates that the agent is a therapeutic agent.

In the Office Action mailed June 15, 2004, the Examiner alleges that, although the specification defines an Alzheimer's disease gene as a homolog of a human gene that has genetic variants associated with an increased risk of Alzheimer's disease or that encodes a gene product associated with Alzheimer's disease and teaches Alzheimer's disease genes, no evidence of record exists that any of the human homologs or gene products have been implicated in Alzheimer's disease (Office Action, paragraph bridging pages 3 and 4). It is further asserted that the specification fails to disclose a parental strain other than *Appl*^{D} that produces test progeny having an altered phenotype (Office Action mailed June 15, 2004, page 4, first full paragraph). Finally, it is asserted that the genes listed on page 14 of the specification are *Drosophila* genes, while the specification fails to identify appropriate parent strains of other organisms (Office Action mailed June 15, 2004, page 4, second full paragraph).

For the reasons set forth below, Applicants submit that, at the time of filing, Applicants had possession of the full scope of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

Contrary to he Examiner's assertion, the specification provides parental strains other than *Appl*^{D} for practicing the claimed invention. The specification discloses numerous Alzheimer's disease genes with which one skilled in the art can practice the invention and further provides additional exemplary Alzheimer's disease genes, including genes disclosed in the specification itself as interacting (directly or indirectly) with *Appl*. Additional Alzheimer's disease genes that are disclosed in the specification, for example at page 14, as useful for practicing the methods of the invention include, for example, *Notch* (N), *Suppressor of Hairless* (Su(H)), *Delta* (Dl), *mastermind* (mam), *big brain* (bib), *halothane resistant* (har38), *cAMP-responsive element-binding protein A* (CrebA), *cAMP-responsive element-binding protein B* (CrebB, activator), *cAMP-responsive element-binding protein B* (CrebB, inhibitor), *α-adaptin*, *garnet* (δ-adaptin), and *shibire* (shi)(dynamin). Furthermore, the specification teaches that an Alzheimer's disease gene can be a gene that is differentially expressed at the mRNA or protein level in *Appl*^{d} flies as compared to *Appl*$^{+}$ flies and discloses several dozen specific examples of such Alzheimer's disease genes in Tables 4-6. One skilled in the art understand would have appreciated that Applicants were in possession of parental strains other than the Drosophila *Appl*^{D}, in sufficient numbers to show possession of the genus of parent strains that carry a mutation in an Alzheimer's disease gene.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Enablement

Applicants traverse the objection to the specification and corresponding rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification sufficiently to enable one skilled in the art to practice the invention.

Briefly, it is asserted that the specification lacks guidance with regard to the particular type of phenotype exhibited by the progeny and how such a phenotype may relate to Alzheimer's disease. The Examiner also asserts that the claims broadly read on transgenic organisms of any species while the specification does not provide commensurate guidance with regard to the preparation of creating transgenic organisms. In this regard, the Examiner cites several references to support the position that transgene expression is unpredictable. A further allegation of non-enablement focuses on the asserted lack of teachings directed to the selection of first parent strains other than *Appl*^{d} and second parent strains in general. Here, the Action points to a lack of guidance with regard to phenotypes that correlate with Alzheimer's disease and provides a further reference, which is alleged to set forth differences in expression of the Drosophila APPL protein and its mammalian homolog, APP.

The specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

The specification teaches that viability is an observable phenotype particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of *Appl*^{d} and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly decreased

viability as compared to sibling controls, while flies carrying *Appl*^{d} and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls.

With regard to a behavioral phenotype, Example III, shows that Appl^{d} Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant change in the physical appearance or observable properties of the test progeny as compared to a sibling control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

With regard to the references provided by the Examiner directed to transgenic techniques, while not conceding non-enablement of transgenic methods, Applicants point out that enablement of every single embodiment within the scope of the claims is not a prerequisite for the enablement of the claimed methods. As taught in the specification, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the invention (page 17, lines 1-10). In this regard, the specification further teaches that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes (*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Therefore, the specification explicitly teaches that the invention methods are contemplated to be practiced via transmission genetics such that the issue of enablement of transgenic methods is tangential to the enablement of the claimed methods. Applicants respectfully submit that the specification conveys to the skilled person that, at the

time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

At the time of filing, those skilled in the art had knowledge that human disease gene homologs had been identified in a variety of genetic systems and, given the broad teachings and guidance for the use and applicability of the claimed methods with regard to species other than Drosophila, would have appreciated Applicants possession of the full scope of the claimed invention. In this regard the specification teaches, for example, at page 17, lines 14-29, homologs of human disease genes in a variety of other genetic systems including zebrafish, nematodes and yeast.

For the various embodiments, the specification provides guidance with regard to practicing the invention in strains corresponding to a variety of genetic systems, for example, at page 39, lines 19-26, which discusses particular modes of administering an agent to mice, nematodes zebrafish and yeast.

With regard to phenotypes useful for practicing the invention, the specification teaches that useful phenotypes include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast. These teachings would have conveyed to the skilled person, at the time of filing, that Applicants, while exemplifying the claimed methods using Drosophila, were in possession of the full scope of their claimed invention, which includes practice of the methods of identifying a therapeutic agent for treating Alzheimer's disease, in strains other than Drosophila and by utilizing transmission genetics.

Finally, with regard to the assertion at page 11 of Paper No. 17, that the Luo et al., *J. Neurosci.* 10(12):3849-3861 (1990) reference supports differences in the structure, regulation and function between the Drosophila APPL protein product and its mammalian homolog APP, Applicants respectfully disagree and point out that, according to the authors themselves, the reference provides evidence supporting the correlation between the Drosophila APPL protein product and its mammalian homolog APP. In this context the Examiner further cites Fossgreen *et al., Procl. Natl. Acad. Sci. USA* 95:13703-13708 (1998), for reporting that the expression of human APP in transgenic Drosophila results in a blistered wing phenotype that the Examiner argues appears unrelated to Alzheimer's disease.

As an initial observation, the presence of any altered phenotype in Drosophila can be related to Alzheimer's disease, given that the gene products are functionally equivalent and that flies are generally not subject to diagnosis with Alzheimer's disease or post-mortem autopsy to determine the presence of amyloid plaques. In this regard, the blistered wing phenotype, although not directly related to Alzheimer's disease, implicates the role of the gene product in cell-cell adhesion, which in turn is certainly related to Alzheimer's disease.

With regard to the Luo reference, the paper concludes its comparative study by indicating "[o]ur results provide further evidence that APP and APPL might be functionally homologous in their respective organisms and suggest an ancestral nervous system function for this class of molecules." (Luo et al., page 3849, right hand column, third paragraph, last sentence). Therefore, according to the authors themselves, the reference provides evidence supporting the correlation between the Drosophila APPL protein product and its mammalian homolog APP. With regard to the Fossgreen *et a*l. reference, Applicants suggest that this reference establishes a γ-secretase activity in insects and acknowledges that this result supports the role of APP in cell adhesion and interaction with integrins, which Fossgreen further acknowledges to be associated with short tem memory in Drosophila and suggestive of a link with "memory mechanisms." (Fossgreen *et al.*, page 13707, right hand column, second

paragraph). Overall, both Luo et al. and Fossgreen et al. support a correlation in both structure and function between the Drosophila APPL protein product and its mammalian homolog APP.

Applicants request that the Office withdraw the objection to the specification and rejection of claims 22-26, 28 and 29 under35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

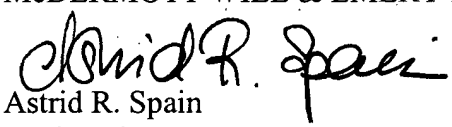
Conclusion

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney with any questions related to this application.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP



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